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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF: Moshe Szyf et al.

Group Art Unit: 1652

Appl. No.: 09/554,414

Examiner: M. Walicka

Filed: September 6, 2000

For: DNA DEMETHYLASE, THERAPEUTIC AND DIAGNOSTIC USES THEREOF

* * * * *

RULE 132 DECLARATION OF MOSHE SZYF

I, MOSHE SZYF hereby declare and say:

5791 Len Banon

M.S.

1. I am a citizen of Canada, presently residing at 7522 Wavell, Côte St-Luc, Quebec, Canada.

2. I am a professor in the Department of Pharmacology and Therapeutics at MCGILL UNIVERSITY, the owner of the above-identified patent application.

3. That my academic background and experiences in the field of the present invention are listed on the enclosed curriculum vitae.

4. I am a co-inventor of the invention described in U.S. Patent Application Serial No. 09/554,414 for "DNA DEMETHYLASE, THERAPEUTIC AND DIAGNOSTIC USES THEREOF" filed September 6, 2000 and I have read and understand the concepts of the specification.

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5. That the following experiments were conducted to demonstrate that (1) the molecules methyl thio-adenosine (MTA) and S-adenosylmethionine (SAM) inhibit active demethylation of DNA, on July 13, 2003 and (2) inhibition of methylated DNA binding protein (MBD2)/demethylase (SEQ ID NO:1) by MBD2/demethylase anti-sense silences urokinase-type plasminogen activator (uPA), presented at the 94th Annual Meeting of the American Association of Cancer Research on July 11-14, 2003.

Experiment 1

Method

The methods for the active demethylation assay are as described in Detich et al. (2003) Journal of Biological Chemistry, 278(23):20812-20820. Briefly, CMV-GFP plasmid is methylated *in vitro* and transiently transfected into HEK 293 cells. Histone acetylation is induced with trichostatin A (TSA), which results in DNA demethylation by endogenous demethylase activity. DNA was extracted from HEK 293 cells and digested first with *EcoRI*, followed by digestion with either *HpaII* or *MspI* restriction enzymes followed by Southern blot analysis using a GFP-specific probe (*AvaII*-*Cf*-101 fragment). The demethylation assay measures the fraction of GFP molecules that were demethylated using *HpaII* restriction enzyme, which cleaves unmethylated CCGG but does not cleave methylated CCGG sequences. The methylated GFP DNA remains intact following *HpaII* digestion and is identical to the fragment obtained following *EcoRI* digestion, whereas the unmethylated GFP DNA is cleaved by *HpaII*.

Results

The Experiment 1 results are illustrated in the attached photograph of the Southern blot (Fig. 1).

MTA and SAM inhibit active demethylation in HEK 293 cells and alter DNA methylation patterns of the GFP gene

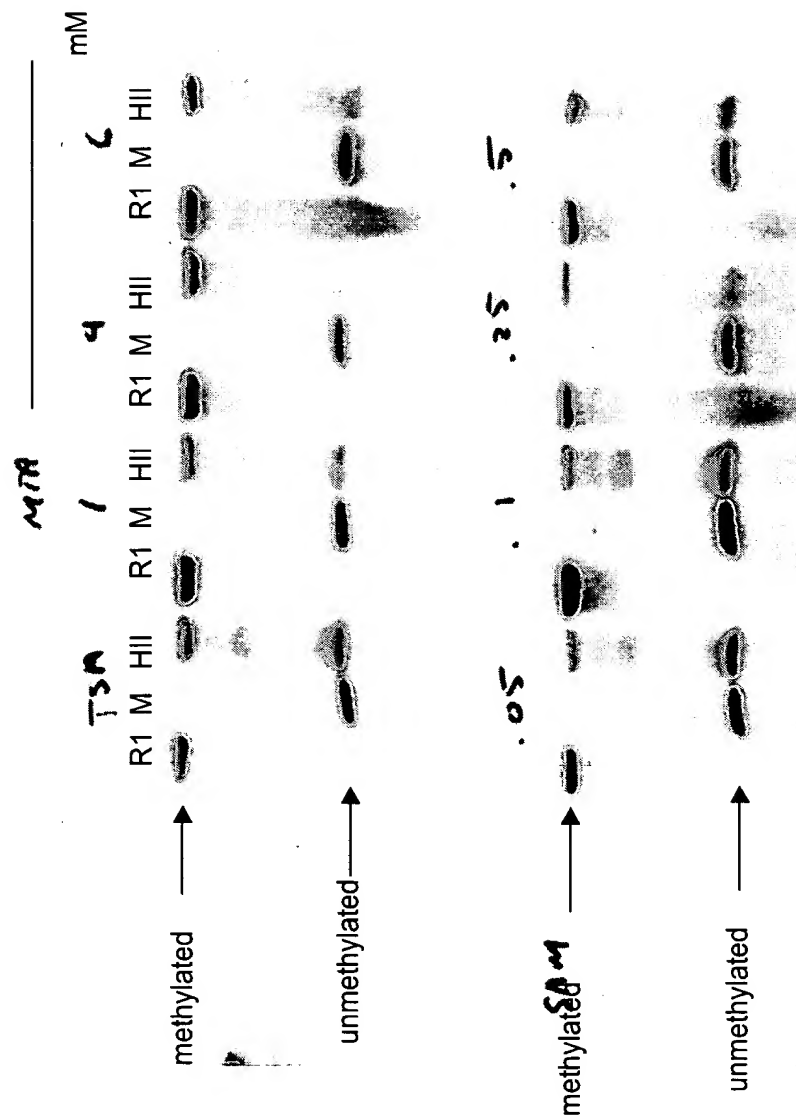


Fig. 1

Active demethylation assay in HEK cells performed as in Detich et al., JBC 278: 20812

R1-EcoR1; M-Msp1; HII-HpaII

Analysis

It can be observed from Fig. 1 that both MTA and SAM inhibit active demethylation of DNA. Specifically, one can observe an increase in methylated DNA, unable to be digested by *HpaII*, in the presence of MTA and SAM.

Experiment 2

Method

The methylation pattern of uPA was determined using methylation specific PCR MS-PCR as described by Herman, et al., 1996, Proc. Natl. Acad. Sci. U.S.A., 93(18):9821-9826, enclosed herewith. Briefly, polymerase chain reactions were performed on bisulfite-modified DNA or unmodified DNA using unmodified (wild-type) primers, methylated-specific primers and unmethylated-specific primers.

Results

The Experiment 2 results are illustrated in the attached figures (Figs. 2 and 3).

Analysis

The inhibition of demethylase results in remethylation and silencing of the uPA gene (Fig. 3A, 3B and 3D). MDA-231 cells have an unmethylated uPA gene as indicated by amplification of the gene with the unmethylated-specific primers but not with the methylated-specific primers. However, treatment of the cells with anti-sense against demethylase (SEQ ID NO:1) results in hypermethylation as indicated by the amplification with the methylated-specific primers (Fig. 3D). Thus, inhibition of demethylase promotes gene silencing.

7. I declare further that all statements made on information and belief are believed to be true, and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the instant patent specification or any patent issuing thereon.

Date: May 6 2004 By: Mentz

Curriculum Vitae

Personal

Date of birth - April 7 1955.
Place of birth- London, England.
Mailing address- Department of Pharmacology and Therapeutics
McIntyre Medical Sciences Building
McGill University
3655 Sir William Osler Promenade
Montreal, PQ H3G 1Y6
Canada

Marital status- Married, three children.

Citizenship- Canadian, Israeli, British

Education

1972-1974- Philosophy and Political Sciences, Bar-Ilan University , Ramat-Gan,
Israel.
1974-1978- Preclinical studies in Dental-Medicine, The Hebrew University,
Jerusalem, Israel.
1978-1980- M. Sc. in Biochemistry, The Hebrew University.
1981-1985- Ph. D. in Biochemistry, The Hebrew University.

Professional Experience

1977-1978- Vice President, The Hebrew University Students Union
1978-1979- President, The Hebrew University Students Union.
1981-1983- Assistant in Biochemistry, The Hebrew University.
1984-1985- Instructor in Biochemistry, The Hebrew University.
1985-1988- Research Fellow in the Department of Genetics, Harvard Medical
school. Boston.
1988-1989- Associate, Howard Hughes Medical Institute, Harvard Medical School.
1989-1993- Assistant Professor, Department of Pharmacology, McGill Medical
School.
1993-2000- Associate Professor, Department of Pharmacology, McGill Medical
School.
2000- present Professor Department of Pharmacology, McGill Medical School.

Awards

1980- M. Sc. with distinction.
1980- The Hebrew University Faculty of Medicine
Award.
1984- Rothschild Fellowship.

1987-	American Cancer Society fellowship.
1989- 1995	National Cancer Institute of Canada, Career Award.
1999-	Elliot Osserman Award for distinguished service from the Israel Cancer Research Fund
1999-	First Carrie Derrick Award for Graduate Teaching and Supervision
2001-	Faculty of Medicine honor list in teaching
2003-	James McGill Professorship

LIST OF PUBLICATIONS

Refereed papers

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 11. Szyf, M. Eliasson, L. Mann, V. Klein, G. & Razin, A.
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 13. Mann, V. Szyf, M. Razin, A. Chriqui-Zeira, E. & Kedar, E.
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 14. Razin, A. Szyf, M. Kafri, T. Roll, M. Gilloh, H. Scarpia, S. Carroti, D. & Cantoni, G. L.
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Submitted for publication

90. Weaver, I. Cervoni, N. D'Alessio, A. C. Champagne, F. A. Szyf, M. and Meaney, J. M.
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91. Pakneshan, P. Szyf, M. and Rabbani, S. A.
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Submitted (2004)
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Alzheimer's disease linked mutations in Amyloid Precursor Protein and Presenilin 1 cause dysregulation of rat hippocampal proteins, potentially involved in learning and memory, long before plaques and learning deficits occur.

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Books and chapters

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2. Neurogenesis and Oncogenesis
"*Restorative Neurology* " Elsevier Science Publishers, Amsterdam. (Cuello, A. C. ed.)" (1993)
3. Szyf, M. Araujo, F. D. Milutinovic, S. Slack, A. D. and Knox, J. D.
How do inhibitors of DNA methyltransferase inhibit cancer cell growth?
V. Workshop on methionine metabolism: Molecular mechanisms and clinical implications."
Eds. Mato, J. M. and Caballero A. University of Navarra Spain pp 75-90 (2000)
supported by CIHR 15626
4. Szyf, M. and Bhattacharya S. K.
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Methods in Molecular Biology **200**, 155-163. (2002)
5. Szyf, M. and Bhattacharya S. K.
Extracting DNA demethylase activity from Mammalian cells.
Methods in Molecular Biology **200**, 155-163. (2002)
6. Szyf, M.
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Encyclopedia of the Human Genome in the press (2003)
Nature Press
7. Szyf, M.

Implications of global hypomethylation on anticancer therapy targeting the DNA methylation machinery

In; DNA methylation and cancer therapy. Ed. M.Szyf Eureka press. 2003

8. Detich, N and Szyf, M.
Regulation of DNA methyltransferases in cancer.
In: DNA methylation and cancer therapy. Ed. M.Szyf Eureka press. 2003
9. Szyf, M.
The bilateral relation between chromatin structure and DNA methylation and its biological role.
Recent Res. Devel. Mol. Cell. Biol. **4**, 39-57 (2003).
10. Cuello, A. C., Bell, K. F. S. Echeverria, V. Lopez, E. Ribeiro-da-Silva, A. and Szyf, M.
The impact of extracellular A β peptides on cortical neurotransmitters and of intracellular accumulation on protein expression.
In; Progress in Alzheimer's and Parkinson's diseases (I. Hanin, Fisher, A. Cocabelos C. eds.) Martin Dunitz, NY (in press)

Book editor:

Szyf, M. Ed. "DNA methylation and cancer therapy" Landers biosciences 2003.

Book review

Szyf, M. "The epigenome" Book review. *Clinical Chemistry* **49**, 9 1 2003.

Szyf, M. Book review *Chembiochem* **3**, 1-3 (2003).

Abstracts

1. Szyf, M. and Tanigawa, G. Cell Cycle regulation of the DNA methyltransferase gene. McGill University Conference on Regulation of Eukaryotic DNA Replication. Montreal, 1990*63.
2. Szyf, M. Milstone, D.S. Schimmer, B. P. Parker, K. L. and Seidman J. G. Silencing of the steroid 21-hydroxylase gene in cultured adrenocortical cells: The role of DNA methylation. ASBMB/AAI Joint Meeting New-Orleans, June 1990. * 1393
3. Szyf, M. Regulation of expression of the DNA methyltransferase gene and its role in maintaining the integrity of a somatic cell. Second New England Biolabs Workshop on Biological DNA Modification. Berlin, Germany, September 1990
4. Rosenzweig, A. Szyf, M. Seidman, J. G. and Seidman, C. E. Mouse P19 cell line expresses atrial natriuretic peptide after induction of Myocyte differentiation. American Federation for Clinical Research meeting, 1990.
5. Rouleau J. and Szyf, M. Characterization of the mouse DNA methyltransferase 5' region reveals a unique housekeeping gene promoter. Canadian Federation Of Biological Sciences Annual meeting. Kingston Ontario, 1991. *511

6. Szyf, M. DNA methyltransferase gene expression is regulated with the Cell cycle and plays a critical role in determining the identity of a somatic cell. Canadian Federation Of Biological Sciences Annual meeting. Kingston Ontario, 1991. *427
7. Abdel-Baset, H. Bozovic, V. Cuello, P. Szyf, M. and Albert P. R. Stimulation of cytosolic calcium levels and DNA synthesis in fibroblasts by 5-HT_{1A} receptors. The Endocrine Society Annual Meeting Washington 1991 *483
8. Szyf, M. and Pinard, M. Designing a binary transgenic mouse system expressing NGF antibody. General meeting NCE neural regeneration and functional recovery. Montreal 1991 *5
9. Szyf, M. Induction of myogenic lineage in 10T1/2 cells harboring a construct expressing sequences encoding the DNA methyltransferase gene in the antisense orientation. The American Society for Cell Biology 31st annual meeting. Boston, Massachusetts, December 8-12, 1991.
10. Albert, P. R., Abdel-Baset, H., Bozovic, V. and Szyf, M. Conditional oncogenesis mediated via a pertussis toxin-sensitive receptor signalling pathway. Seventieth EMBO symposium Heidelberg, Germany, 1991.
11. Szyf, M.
Induction of myogenic differentiation by a DNA methyltransferase antisense
Proceedings of 3rd International Conference on Role of Formaldehyde in Biological Systems: Methylation and Demethylation Processes,
Tyihak, E. Editor The Hungarian Biochemical Society, 1992, p.p. 48-53.
12. Rouleau, J. and Szyf, M.
Regulation of the mouse DNA methyltransferase by signal transduction pathways.
1992 ASCB annual meeting, Denver Colorado. #01386
13. Odeh, R., Philie, J., Szyf, M., and Quik, M.
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Society for Neuroscience Abstracts , Volume 18, #189.4, 1992.
14. MacLeod, R. A., Bozovic, V., and Szyf, M.
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The American Society For Cell Biology #00325
New-Orleans December 1993.
15. Rouleau, J., Bozovic, V., and Szyf, M.
Transformation of mouse C2C12 cells by RAS is inhibited by an antisense RNA to the DNA methyltransferase.
The American Society for Cell Biology #00226
New-Orleans December 1993
16. Szyf, M., and Theberge, J.

Mammalian cells contain a general (CpG) DNA demethylating activity.
The American Society for Cell Biology #426
New-Orleans 1993.

17. Szyf, M. MacLeod, R. A. and Rouleau, J.
Regulation of DNA methylation by oncogenic signal transduction pathways.
Third New-England Biolabs Workshop on biological DNA modification. (18#)
Villnius, Lithuania, 1994.
18. Huang, D. C., Pinard, M., Szyf, M. and Cuello, A. C.
Cloning and nucleotide sequence analysis of anti-NGF antibody gene.
NCE Network for neuronal regeneration and recovery annual meeting.
Toronto, Ontario. June 1994.
19. Huang, D. C., Pinard, M., Szyf, M. and Cuello, A. C.
Cloning and expression of an antibody against rat NGF.
Society for Neuroscience annual meeting Miami Beach Florida
November 1994.
20. Ramchandani, S. K., Rouleau, J., and Szyf, M.
Cloning of the Human DNA methyltransferase gene.
American Society for Human Genetics.
Montreal Quebec October 1994.
20. Szyf, M.
Induction of a general CpG DNA demethylating activity by the ras signaling
pathway in mouse embryonal cells.
The American Society for Cell Biology
San-Francisco, December, 1994. #497
21. MacLeod, A. R. and Szyf, M.
Regulation of DNA methylation by the Ras signaling pathway
The American Society for Cell Biology
San-Francisco, December, 1994. #2054
22. Grant, S. M. Szyf, M. and Cuello, A. C.
Engraftment of P19 cells overexpressing hAPP751 into rat entorhinal cortex.
Society for Neuroscience 1995.
23. Ramchandani, S., MacLeod, A. R., von Hofe, E. and Szyf, M.
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tumorigenesis.
American Association for Cancer Research, Washington 1996.
24. Ramchandani, S. and Szyf, M.
A novel RNA element mediates the cell cycle dependent posttranscriptional
regulation of DNA methyltransferase.
The American Society for Cell Biology
San-Francisco, December 1996.

25. Pinard, M. and Szyf, M.
Regulation of cytosine DNA methyltransferase expression by tumor suppressors.
The American Society for Cell Biology
San-Francisco, December 1996.
26. Araujo, F., Szyf, M., Price, G. B. Zannin-Hadjopoulos, M.
Methylation kinetics on origins of replication
Eukaryotic DNA replication (Cold Spring Harbor Laboratory September 1997)
27. Knox, J. D., Bigey, P. Boreham, DB., Szyf, M.
The inhibition of DNA methyltransferase by an oligonucleotide slows but does not
arrest the growth of A549 cells in vitro.
AACR Special Conferences Puert Rico 1997
28. Gordon Research Conference on Purines, Pyrimidines & Related substances of
1995 Salva Regina University July 2-7 1995 Discussion Leader
29. Vermont Academy, June 14-19 1997
FASEB Summer Resaerch Conference Biological methylation
30. Copsis, Greece August 17-25, 1997. International conference on
genetherapy/chromatin (supported by NCI)
31. Iglis, Austria september 2 to 7 1997. Fourth New England Biolabs Workshop on
biological DNA modification.
32. Szyf, M. DNA Methyltransferase: a downstream effector of oncogenic programs;
implications for therapy. International conference on gene
therapy/chromatin
Copsis Greece August 17-25 1997
33. Szyf, M. Ramchandani, S. Bhattacharya, S. and Knox, D. The enzymes of the
cytosine DNA methylation machinery as anticancer targets
Copsis, Greece August 9-15, 1998. International conference on gene
therapy/chromatin (supported by NCI)
34. Bhattacharya, SF., Ramchandani, S. and Szyf, M. DNA demethylase: a novel
enzyme playing a critical role in development and oncogenesis.
4th International Conference on Role of Formaldehyde in biological systems;
methylation and demethylation processes
Budapest, Hungary July 1-4 1998 (supported by NCI)
35. Moshe Szyf, Shyam Ramchandani and Sanjoy Bhattacharya
The DNA methylation machinery as an anticancer target.
Curie Workshop on epigenetics and DNA methylation.
Paris 23-26 September 1998. (supported by NCI)
36. Knox, D. Araujo, P. Bigey, P. Knox, D.
DNA replication and methylation.
Regulation of DNA replication

October 15-18 1998
Saint-Sauver-desMonts, Quebec

37. Szyf, M. Ramchandani, S., Milutinovic, S. and Bhattacharya, S.
The DNA methylation machinery as an anticancer target.
Gene Therapy and Molecular Biology & Medicine International Conference
Cassis, Crete, Greece # 248.
38. Szyf, M.,
DNA methyltransferase (DNMT1) inhibitors are candidate anticancer agents.
VIII International conference on Differentiation therapy
October 3-6, 1999 Montreal, Canada #093.
39. Szyf, M.
The DNA methylation machinery as an anticancer target.
Colorectal cancer: New aspects of Molecular Biology, Immunology and clinical
applications.
Berlin, Germany 8-9 October 1999. #17
40. Szyf, M.
DNA methylation and cancer
Workshop on Methionine Metabolism Molecular mechanisms and Clinical
implications.
February 21 2000
Sierra Nevada Granada Spain
41. Szyf, M.
DNA methyltransferase and demethylase.
American Gastroenterological Association meeting May 21-24. San Diego 2000
S266.
42. Szyf, M.
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coordinating silencing of tissue specific gene expression and cancerous growth in
adrenal carcinoma cell line Y1.
IXth Adrenal Cortex Conference Toronto 17-20 (2000) p166
43. Szyf, M.
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Gene, Drug Therapy and Molecular Biology Rhodes Greece August 26-31 2000 p 36
43. Szyf, M. and Detich, N.
The role of DNA methyltransferase 1 in growth control
Regulation of DNA replication
April 6-8 2001
Saint-Sauver-desMonts, Quebec
46. Szyf, M. and Detich, N.
The role of the DNA methylation machinery in growth control and cancer.

Gene, Drug Therapy and Molecular Biology Corfu Greece August 26 2001

47. Weaver I, Cervoni, N, Diorio J, Szyf, M, and Meaney, MJ.
Maternal behavior in infancy regulates methylation of the hippocampal glucocorticoid receptor promoter.
Gene, Drug Therapy and Molecular Biology Corfu Greece August 26 2001
48. Weaver I, Cervoni, N, Diorio J, Szyf, M, and Meaney, MJ.
Maternal behavior in infancy regulates methylation of the hippocampal glucocorticoid receptor promoter.
Society for Neuroscience (6917.15.2001) San Diego November 2001
49. Szyf, M., Detich, N., Cervoni, N., Bovenci, V., and Zhuan, Q-L.
Maintaining the integrity of the epigenome: integrating dna replication, dna methylation and chromatin structure.
6th Lake Tahoe Symposium Lake Tahoe California, 2002.
50. Weaver, I. C. G. Cervoni, N. Szyf, M. and Meaney, M. J.
Maternal behavior in infancy regulates methylation of hippocampal glucocorticoid receptor promoter.
Society for Neuroscience (8669.9.2002) Orlando Florida 2002
51. Cuello, A.C., Echeverria, V., Dowd, E., Lopez, E., Vercauteren, F., Bell, K., Ribeiro-da-Silva, A. and Szyf, M.
The impact of Intracellular A-beta peptides
The 11th Annual Meeting of the Israel Society for Neuroscience, Eilat, Israel, December 15th, 2002.
52. Bovenzi, V. Milutinovic, S Ren, H. and Szyf, M.
Differential regulation of MBD2/demethylase expression during cellular differentiation and transformation.
American Association for Cancer Research 94th Annual Meeting 2003
#77
53. Pakneshan, P. Szyf, M. and Rabbani, SA
A 20 mer antisense oligo against MBD2/demethylase causes a marked decrease in urokinase (uPA) expression and blocks breast cancer progression in vitro and in vivo.
American Association for Cancer Research 94th Annual Meeting 2003
#3359
54. Cuello, A.C., Echeverria, V., Bell, K.F.S., Lopez, E., Ribeiro-da-Silva, A. and Szyf, M
The impact of extracellular A-beta peptides on cortical neurotransmitters and of its intracellular accumulation on protein expression
6th International Conference on AD/PD, Seville, Spain, May 8-12, 2003
55. Cuello, A.C., Echeverria, V., Dowd, E., Lopez, E., Vercauteren, F., Bell, K.F.S., Ribeiro-da-Silva, A. and Szyf, M.
The impact of intracellular a-beta peptides. The 11th Annual meeting of the Israeli Society for Neuroscience, Eilat, Israel, December 15th, 2002.

56. Ou, J-N. Hamm, S, Mamer, O, Just, G, and Szyf, M.
Characterization of the demethylase activity of MBD2 in living cells and in vitro.
American Association for Cancer Research 94th Annual Meeting 2003
#5813
57. Szyf, M.
The DNA methylation Machinery in cancer and anticancer therapy
Meet-the Expert sunrise session
American Association for Cancer Research 94th Annual Meeting 2003
58. Moshe Szyf, Ian C.G. Weaver, Nadia Cervoni, Ana C. D'Alessio, Frances A.
Champagne, and Michael J. Meaney
Word Congress Of Psychiatric Genetics
Quebec City Quebec October 2003
59. Weaver, I. C. G., Champagne, F. A. D'Alessio A. C., Sharma, S., Dymov, S., Meaney
M. J., and Szyf Moshe.
Reversal of Maternal Programming of stress responses through modulation of the
epigenome.
American Society of Neurosciences annual Meeting 2003.

60.

Presentations in International Symposia

1. Berlin, September 1990. Second New England Biolabs Workshop on Biological
DNA Modification.
2. Sopron, Hungary 1992. 3rd International Conference on Role of Formaldehyde
in Biological Systems: Methylation and Demethylation Processes,
3. Copper Mountain, Colorado August , 1993. Biochemistry and Pharmacology of S-
Adenosylmethionine and Methylation.
4. Villnius, Lithuania, May 1994. Third New England Biolabs workshop on
biological DNA modification.
5. Gordon Research Conference on Purines, Pyrimidines & Related substances of
1995 Salva Regina University July 2-7 1995 Discussion Leader
6. Vermont Academy, June 14-19 1997
FASEB Summer Research Conference Biological methylation
7. Capsis, Greece August 17-25, 1997. International conference on gene
therapy/chromatin
8. Igls, Austria September 2 to 7 1997. Fourth New England Biolabs Workshop on
biological DNA modification.

9. Szyf, M. DNA Methyltransferase: a downstream effector of oncogenic programs; implications for therapy. International conference on gene therapy/chromatin
Capsis Greece August 17-25 1997
10. Szyf, M. Ramchandani, S. Bhattacharya, S. and Knox, D. The enzymes of the cytosine DNA methylation machinery as anticancer targets
Capsis, Greece August 9-15, 1998. International conference on gene therapy/chromatin
11. Bhattacharya, SF., Ramchandani, S. and Szyf, M. DNA demethylase: a novel enzyme playing a critical role in development and oncogenesis.
4th International Conference on Role of Formaldehyde in biological systems; methylation and demethylation processes
Budapest, Hungary July 1-4 1998
12. Moshe Szyf, Shyam Ramchandani and Sanjoy Bhattacharya
The DNA methylation machinery as an anticancer target.
Curie Workshop on epigenetics and DNA methylation.
Paris 23-26 September 1998.
13. Knox, D. Araujo, P. Bigey, P. Knox, D.
DNA replication and methylation.
Regulation of DNA replication
October 15-18 1998
Saint-Sauver-desMonts, Quebec
14. Capsis, Greece August 7-15, 1999. International conference on gene therapy/chromatin
15. International Conference on Differentiation therapy
Montreal Canada October 3-6 1999
16. Berlin Germany "Colorectal Cancer"
8-9 October 1999.
17. Workshop on Methionine Metabolism Molecular mechanisms and Clinical implications.
February 21 2000
Sierra Nevada Granada Spain
18. Symposium speaker; American Gastroenterological Association
May 23 2000
San Diego, California
19. Plenary speaker: International conference on gene therapy and molecular biology.
Rhodes, Greece August 31 2000.
20. Regulation of DNMT1 and the cell cycle. DNA replication conference.
St. Sauver Quebec April 6 2001

16. Plenary speaker: International conference on gene therapy and molecular biology.
'Corfu, Greece August 26 2001.
The role of the DNA methylation machinery in growth control and cancer.
17. 6th Lake Tahoe symposium on molecular diversity.
Lake Tahoe, California January 28-February 1 2002.
18. "Cancer Epigenetics: DNA Methylation and Chromatin"
Madrid, Spain May 29-31 2002
19. Annual Conference of the American Associations of Cancer Research, Meet-the
Expert Sunrise Session speaker on ; DNA methylation and cancer April 2003.
20. Symposium speaker : "Mechanisms integrating histone acetylation and DNA
methylation"
Experimental Biology April 11-15 2003 San Diego California #S552
21. Epigenetic mechanisms, gabaergic neurotransmission, reelin and psychosis"
Santiago de Compostela, June 14-16 2003. Aula Magna, School of Biology, Spain
22. Seoul Cancer Symposium Seoul Korea, September 26 2003. (represented by Ian
Weaver)
23. Szyf, M.
Transgenerational epigenomic imprinting by maternal behavior through DNA
methylation and its reversal by histone deacetylase inhibitors
Word Congress Of Psychiatric Genetics
Quebec City Quebec October 2003
24. Szyf, M.
Nobel symposium on epigenomics
Karolinska institute
Stockholm Sweden June 22-26 2004.
25. Szyf M.
DNA methylation and breast cancer
Chromatin structure and gene expression mechanisms as therapeutic targets
European Conference Center (Luxembourg) January 28 - 31, 2004

Seminars and International Presentations

1. Interdisciplinary Endocrine Seminars, Royal Victoria Hospital Nov 1, 1990
2. Department of Anatomy, McGill University May 22, 1991.
3. Department of Physiology, McGill University, October 11th 1991.
4. Department of Microbiology and Molecular Genetics, Burlington, Vermont State
University, November 13th 1991.
5. Hybridon, Worcester, Massachussets, March 17th 1992.
6. Department of Microbiology, Sherbrooke University, Nov 19th 1992.
7. Research Seminar Series at the Montreal Children's Hospital, April, 26 1993.
8. Department of Cellular Biochemistry, Hebrew University Jerusalem Israel July 18 1993
9. Hybridon, Worcester MA. October 1993.
10. Ontario Cancer Institute Toronto Ontario March 3rd 1994.

11. Montreal Molecular Genetics group meeting April 26 1995
12. Seminars in Surgical Research, McGill University, December 18 1995.
13. Hybridon, Worcester MA October 1995.
14. McGill cancer Center February 6 1997.
15. Department of Cellular Biochemistry, Hebrew University Jerusalem July 1997
16. Janssen Research Foundation, September 1 1997.
17. Department of Biology University of Rochester Rochester New York April 20 1998.
18. NIH, Therapeutic oligonucleotides group seminar. NIH Bethesda Maryland May 28 1998.
19. Department of Biochemistry, Hebrew University, Jerusalem, Israel. July 8 1998.
20. Small Molecule Therapeutics, Inc. Monmouth Junction New Jersey April 12 1999.
21. Children's Hospital, Montreal April 19, 1999.
22. Janssen Research Foundation, Beerse Belgium April 22, 1999.
23. Department Exploratory Research, Boehringer Ingelheim Austria April 30 1999.
24. Division of Cancer Biology Research Seminar, Sunnybrook, Health Science Center Toronto, Canada June 9 1999.
25. Biotechnology Research Institute, Montreal June 23 1999.
26. Center De Recherche de Vitry-Alfortville, Rhone-Poulenc Rorer France, July 9 1999.
27. Department of Cellular Biochemistry, The Hebrew University Israel August 5 1999.
28. Molecular Endocrinology Royal Victoria Hospital, October 21 1999.
29. Department Physiology, McGill University, October 29 1999.
30. Douglas hospital, Montreal "How does DNA methyltransferase transform cells?" 15/11/99
31. Centre De Recherche De L'Hopital Sainte-Justine 21/1/2000 How does DNA methyltransferase cause cancer?
32. Notre dam hospital university of Montreal, Montreal, "DNA methylation" March 31 2000.
33. Department of Anatomy and Cell biology, McGill University How does DNA methyltransferase cause cancer? March 25, 2000
34. Department of Pharmacology McGill University, How does DNA methyltransferase cause cancer? 4/4/2000.
35. Department of Chemistry and Biochemistry University of Texas, How does DNA methyltransferase cause cancer? Austin Texas, May 12 2000.
36. NIH section of Molecular Pathology National Institute of Allergy and Infectious Diseases September 7 2000.
37. Department of Biology McGill University January 29 2001.
38. Cancer Center McGill University February 8 2001.
39. Neuroscience Research Institute, Ottawa, February 26 2001.
40. McMaster University, MOBIX November 1 2001. Maintaining the integrity of the epigenome.
41. University of Toronto, Toronto Western research institut, December 4 2001, Maintaining the integrity of the epigenome.
42. University of Montreal, department of Pharmacology 17 January 2002 : maintaining the integrity of the epigenome : Integrating DNA methylation, DNA replication and chromatin structure.
43. University of Illinois at Chicago, the psychiatric Research Institute February 6 2002: Maintaining the integrity of the epigenome; Integrating DNA replication, DNA methylation and chromatin structure.
44. Max-Delbrück Research Center in Berlin May 7 2002: Integrating chromatin structure, gene expression and DNA methylation, the role of demethylase.

45. Department of Biochemistry McGill University. September 19 2002. The bilateral interrelationship of chromatin and DNA methylation.
46. Childrens Hospital Research Institute Montreal Quebec February 10 2003; the dynamic epigenome.
47. University of Paris faculty of pharmacology: The dynamic epigenome and its implications on cancer and behavior June 18 2003
48. Department of Microbiology and Molecular Cell Biology Eastern Virginia Medical School
Norfolk Virginia November 11 2003.

Patents and patents filed

1. U.S. patent, 5,578,716 date filed: December 1 1993. with Dr. Van Hoffe Hybridon: DNA methyltransferase antisense oligonucleotides
2. U. S. patent 5,591,772 Antisense oligonucleotides having tumorigenicity inhibiting activity.
3. U. S. patent 6,054,439 antisense oligonucleotides having tumorigenicity inhibiting activity.
4. U. S. patent 6,184,211 Inhibition of DNA methyltransferase
5. U. S. patent 6,066,625 Optimized antisense oligonucleotides complementary to DNA methyltransferase sequences.
6. PCT Antisense oligonucleotides having tumorigenicity-inhibiting activity
International Publication number: WO95/15378
7. PCT Inhibition of DNA methyltransferase International publication number: WO 95/15373 Patent allowed in Europe (1999)
8. U.S patent application: Specific inhibitors of DNA MeTase (Filed May 1996)
Docket Number: 106.101.120
9. Modified oligonucleotides as bona fide antagonists of proteins interacting with DNA: Hairpin antagonists of the human DNA MeTase PCT/1B97/00879 WO 9744346.
10. DNA methyltransferase genomic sequences and antisense oligonucleotides. US patent application (Ref. 106101.187) (May 5 1997). Patent allowed 2000
11. DNA demethylase, therapeutic and diagnostic uses thereof. (Canada) November 11 1997 1770-183.
12. DNA demethylase cDNA (Canadian patent application)
13. DNA demethylase therapeutic and diagnostic uses thereof PCT 1770-183 PCT
14. DNA demethylase therapeutic and diagnostic thereof US patent application 09/554,414.

Funding

1985-1986-Rothschild Foundation	19,000
1986-1988-American Cancer Society	19,500 (per year)
1989-1990- National Cancer Institute equipment award-	50,000
1989-1995-National Cancer Institute Career Award-	52,940 (per year)
1989-1992-National Cancer Institute Operating Grant	74,592 (per year)
1991-1993-Cancer Research Society Operating Grant	50,000 (per year)
1991-1994-MRC	70,629 (per year)
1993- -National Cancer Institute equipment award	9,000
1993-1996-National Cancer Institute Operating Grant	102,000 (per year)
1992-1994-Center of Excellence for neural regeneration Cuello)	23,000 (per year)(with Dr.
1992-1994-Center of Excellence for neural regeneration Cuello	50,000 (per year) (with Dr.
1993-1995-Cancer research society	50,000 (per year)
1994-1997-NCI	66,000(per year)
1996-1999-NCI	66,000(per year)
1996-1999 MRC	76,118 (per year)
1997 MRC (equipment grant)	89,500
1997-2000(NSERC)-	145,500 (PA) declined) 1999-2002
(MRC)-	67,217
1999-2002- (NCIC)-	85,860
1999-2002 (NCIC)-	112,970
2002 (CIHR-proof of principle)	115,000
2000-2005 (CIHR)	111,280
2002-2007 (NCIC)-Regulation of DNA MeTase	142,548
2002-2007 (NCIC) –Analysis of demethylase	139,275
2002-2006 (NIH, selley PI)	67,000 (my component)
2002-2007(CIHR coPI with Meaney)	80,000 (my component)

Industrial Support

Hybridon, Worcester MA	250,000 P.A (1992-1996)
1996-1998-MethylGene	250,000 P.A. (1996-1997)

Other activities

Ad hoc consulting- Medical Science Partners, L. P. Brookline, MA.
 Consultant- Medicorp, Montreal PQ.
 Member National Cancer Institute grant review panel G- Pharmacology, Carcinogenesis, and Chemistry. (1993-)
Chair - National Cancer Institute grant review panel G- Pharmacology, Carcinogenesis, and Chemistry. (1995-)
 Member Scientific Advisory Board-MethylGene
 Member scientific Review Board Israel Cancer Society (1996-1999)
 Member Medical Research Council Pharmacology grant review panel (1998-)
 Member Scientific Advisory Board Israel cancer society (1999-)

Societies

Pharmacological Society of Canada
 American Society for Microbiology

American Society for Cell Biology

Editorial position

Chief editor Current Drug Targets 2000-

Ad hoc reviews for:

DNA, Molecular and Cellular Biology, Cancer research, Theriogenology, Gastroenterology, Clinical and Journal of Laboratory and Clinical Medicine, Differentiation, MRC, NCI RSQ FCAR NSERC. The Israel Science Foundation, Ontario mental health foundation, Canadian Breast cancer foundation, International Union against Cancer

Inter-University Teaching

Basic molecular Biology, Montreal Heart Institute, May-June 1992.

Committees

1994- 1999-Faculty Postgraduate Awards Committee

1997- present University TENURE COMMITTEE/Agriculture

1999- Advisory Committee for the selection of a Dean of Science (alternate)

2000- Search Committee for Chair of Pharmacology

2000-present- Member graduate studies committee, Department of Pharmacology

1991-1996 Chairman, Library Committee

1997-present Chair, Equipment Committee

1992- Member, Peptide Pharmacologist Search Committee

1990-1995 Coordinator, Faculty Journal club.

1990-1993-Chairman, Library Committee

Service to the Community

1991-1997 Weekly Bible class Hebrew Academy Cote St.Luc

1997-present Daily Talmud Class Rinat Israel Congregation Cote St. Luc Quebec

1997-present Cantor, High Holiday Services Rinat Israel Congregation Cote St. Luc Quebec.

September 15 1998- Key Note Speaker Israel Cancer Research Fund, Montreal Chapter.

March 14 1999- Discussion host at the Bell Montreal High School Research Science Fair at the Pierre Fonds Comprehensive High School

15, 16 April 1999- Premier Bouchard delegation to New York

!6 April 1999- Lecturer at the Symposium organized by the Quebec delegation to NY at the Columbia Presbyterian Center

July 1999- Member Advisory Board of the first international Think Tank Conference on Tal-Am (New Hebrew Studies Curriculum in Jewish Day Schools)

July 23 1999 Lecture at the International conference of Jewish Day School Principals (Tal Am Think Tank) Jerusalem Israel

July 25 1999 Lecture at the International conference of Jewish Day School Principals (Tal Am Think Tank) Jerusalem Israel

September 2003

A seminar series at the Jewish Public Library on;

Navigating the enchanting waters of the high holidays liturgy.